Determination of the Levels of Anti-Thyroid-Stimulating Hormone Receptor Antibody with Thyroid Peroxidase Antibody in Omani Patients with Graves' Disease

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Key Words

Graves' disease · Anti-thyroid-stimulating hormone receptor antibody · Thyroid · Autoantibody · Thyroid peroxidase antibodies

Abstract

Objective: To determine the levels of anti-thyroid-stimulating hormone receptor antibody (TRAb) and thyroid peroxidase antibodies (TPO) in Omani patients with Graves' disease (GD). **Subjects and Methods:** ELISA was used to measure the levels of TRAb and TPO in sera of 111 patients with GD, 40 patients with systemic lupus erythematosus (SLE) and 50 healthy normal subjects. Seventy-eight GD patients received iodine-131 treatment while 33 newly diagnosed patients did not receive any treatment. **Results:** The levels of TRAb in the patients with GD, SLE and normal subjects were 7.24 ± 0.623 , 1.04 ± 0.179 and 0.539 ± 0.070 units/liter, respectively. Elevated levels of TRAb were found in 75, 5 and 2% of patients with GD, SLE and normal subjects, respectively. For anti-TPO antibodies, the levels were 713.331 ± 97.905 , 85.575 ± 34.936 and 22.96 ± 4.544 IU/ml, for patients with GD, SLE and normal subjects, respectively. The elevated level of anti-TPO antibodies were found in 72, 15 and 6% of patients with GD, SLE and normal subjects. Statistically significant differences in positive lev-

els of TRAb and anti-TPO antibodies were found in patients with GD as compared to SLE and normal subjects ($p < 0.001$). The treated GD patients had lower levels of TRAb than untreated, but no difference was detected in the levels of anti-TPO antibodies between the treated and not treated. **Conclusion:** High levels of TRAb and TPO were detected in Omani patients with GD. TRAb may be helpful in the diagnosis and monitoring the efficacy of iodine-131 treatment in GD patients.

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Introduction

Abnormal autoimmune reactions to thyroid-specific proteins, including the thyroid-stimulating hormone (TSH) receptor, thyroglobulin, and thyroid peroxidase (TPO), in autoimmune thyroid diseases such as Graves' disease (GD) have been the subject of interest by many investigators [1, 2]. The TSH receptor plays an important role in the function and growth of thyroid cells [3]. GD is thought to result from the production of autoantibodies to the TSH receptor (TRAb). Binding of these autoantibodies to the TSH receptors causes stimulation of thyroid cells and overproduction of thyroid hormones, resulting in hyperthyroidism [4]. TRAb is a well-known marker for thyroid gland autoimmunity and thus may have predic-

tive value in the recurrence of GD after treatment with antithyroid drugs [5]. This antibody has been reported to be present in more than 80% of GD patients and thus may activate thyroprotein receptors and produce clinical thyrotoxicosis [6].

Consequently, the measurement of TRAb could be valuable for the differential diagnosis of hyperthyroidism as well as for the follow-up of GD patients receiving antithyroid drugs, such as iodine-131 sodium iodide (^{131}I) or surgery. The presence of TRAb may also help in distinguishing GD from other causes of thyrotoxicosis such as factitious thyrotoxicosis and other causes of hyperthyroidism like subacute or postpartum thyroiditis and toxic nodular goiter.

The study of GD has been facilitated by the identification of dominant specific target antigens for TRAb and TPO antibodies [4, 7]. These antibodies are now routinely measured in suspected GD to confirm the diagnosis of autoimmune thyroid disease. Thus, the objective of this study was to determine the levels of TRAb and TPO antibodies in Omanis with GD, systemic lupus erythematosus (SLE) and normal subjects.

Subjects and Methods

Subjects

The study included 111 adult Omani subjects (75 females and 36 males) with a clinical diagnosis of GD (age range 16–66 years, average 32.4 years). Seventy-eight of them received ^{131}I treatment while 33 newly diagnosed patients did not receive any treatment. A further 40 patients with SLE (as autoimmune nonthyroid controls) and 50 healthy control subjects were included in the study. GD, SLE patients and control subjects were matched in terms of age and sex. Sera from all the subjects were screened for the presence of TRAb and TPO antibodies.

Measurement of TRAb

Circulating levels of TRAb were measured with a commercial ELISA kit (Medizym T.R.A., Medipan Diagnostica, Germany) according to the manufacturer's instructions. Values of >2 units/l were considered as positive as set by the manufacturer.

Measurement of TPO

An ELISA assay (Medizym anti-TPO, Medipan Diagnostica) was employed for the quantitative measurement of human TPO antibodies in serum. A standard ELISA technique was employed using buffers and reagents supplied with the kit. All procedures were performed according to manufacturers' instructions. TPO antibody values of >30 IU/ml were considered as positive.

Statistical Analysis

Statistical analysis was performed using χ^2 test from SPSS for windows program. A p value <0.05 was considered as significant.

Fig. 1. Percentage of Omani patients with GD screened for serum antibodies to TRAb and TPO antibodies in comparison to those derived from normal controls and patients with SLE.

Results

Elevated TRAb levels were found in 75% of patients with GD (7.249 ± 0.623 units/l; mean $\pm$ SE), in 5% of patients with SLE (1.024 ± 0.179 units/l; mean $\pm$ SE) and in 2% of normal subjects (0.539 ± 0.070 units/l; mean $\pm$ SE). As for anti-TPO antibodies, the values were found to be 72% of patients with GD (713.331 ± 97.905 IU/ml; mean $\pm$ SE), 15% with SLE (85.575 ± 34.936 IU/ml; mean $\pm$ SE) and 6% of normal subjects (22.96 ± 4.544 IU/ml; mean $\pm$ SE) (fig. 1). Positive sera for both TRAb and TPO were significantly higher in GD patients as compared to SLE patients and normal subjects ($p < 0.0001$). No difference was found between gender and age.

As shown in figure 2, GD patients receiving ^{131}I treatment had a significantly lower level of TRAb than the nontreated patients ($p < 0.005$). Positive levels were found in 42.5 and 88.5% of the treated and nontreated patients, respectively. No difference was observed between positive TPO values of the treated (70%) and untreated (75%) patients.

No correlation ($r = 0.14$; $p = 0.13$) was found between the levels of TRAb and TPO antibody.

Fig. 2. Comparison between treated and untreated groups of Omani patients with GD who are positive for TRAb and TPO antibodies.

Discussion

TRAb is a well-known marker of thyroid gland autoimmunity. It has been reported to be the direct cause of hyperthyroidism in GD patients and one of the best examples of pathogenic autoantibodies [4]. The level of TRAb is measured routinely to confirm the diagnosis of GD and many authors have reported high levels of TRAb in GD patients [6, 8–10] similar to our results.

Earlier investigations had suggested that TRAb levels tend to fall during antithyroid drug treatment, which may have some predictive and prognostic value in the recurrence of GD after treatment [5, 11, 12]. Our study has confirmed this observation as evidenced by the significantly lower TRAb level in treated patients as compared to the untreated group. The post-treatment decline in TRAb levels may indicate that the patient's thyrotoxicosis is of an autoimmune etiology rather than due to other causes.

Our study showed no statistical differences in TPO levels in the treated and untreated GD patients. An earlier report had shown an increase in serum levels of TPO after treating patients with ^{131}I [13] while another showed a decrease [14]. These variations may be due to differences in the immunological response caused by a decline in disease activity or a direct effect of the drug.

Of most interest, in the current study, is the absence of a statistically positive correlation between the levels of TRAb and TPO autoantibodies in GD patients, which is not consistent with a previous study [15] that had reported such a correlation. The differences in the two studies may be due to the nature of GD pathogenesis [16], to the number of subjects studied or different assays used as well as genetic and environmental factors. Patients with SLE in this study, representing a nonthyroid autoimmune disease, had higher levels of TRAb and TPO antibody than normal subjects, similar to other studies [17, 18].

The level of TRAb and anti-TPO among the general population in Oman is not known. Our findings have shown that the corresponding values are 2 and 6% in 50 normal subjects. This number is too small to draw any conclusion such as prevalence rates. However, the estimated prevalence of TPO antibodies among the general population in other studies has been shown to be as high as 15% [15, 19] and rises with age [20].

Conclusion

This study shows high levels of TRAb in Omani patients with active GD and a lower, but significant, level in patients treated with ^{131}I . Similarly, the level of TPO antibodies was high in GD patients, though it did not correlate with that of TRAb.

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